

III: THERAPEUTICS

AREA OF EMPHASIS:

Therapeutics

SCIENTIFIC ISSUES

Basic research on the viral life cycle, pathogenic mechanisms, and host-virus relationship continues to provide a strong foundation for the design, development, and evaluation of improved treatment regimens for HIV infection and its associated coinfections, opportunistic infections (OIs), and malignancies. The NIH supports a comprehensive AIDS therapeutics research program with the goal of developing new and better approaches to prevent, treat, and control HIV infection and its sequelae. The use of antiretroviral therapy (ART) continues to result in the significant reduction of viral load, increased CD4 cell counts, decreased OIs and certain malignancies, and improved immune function in patients who are able to adhere to the treatment regimens and tolerate the toxicities associated with antiretroviral (ARV) drugs.

A high priority of NIH-sponsored AIDS therapeutics research continues to be the development of better drugs and therapeutic regimens that are less toxic and have fewer side effects, limit the development of drug resistance, enter viral reservoirs to inhibit viral replication, promote easier adherence, and are more readily accessible. The global impact and continued spread of the AIDS pandemic in both developed and developing nations underscore the urgent need to develop therapeutic regimens that can be appropriately implemented in international settings.

The scientific agenda for NIH AIDS therapeutics research is focused upon answering the following questions:

- Are there new viral and cellular targets against which therapies can be directed?
- What therapeutic agents and regimens can be developed that target drug-resistant virus and have activity in viral compartments and cellular reservoirs?
- What are the optimal therapeutic approaches for management of HIV infection, including when to start, change, sequence, or interrupt therapy?
- How can the pharmacologic and toxicologic properties of these agents be improved?
- What are the pharmacokinetics of these drugs in pregnant and breastfeeding women, and what impact does this have upon the fetus?
- What are the immunologic determinants to predict the efficacy of immune-based therapies?
- What is the impact of coinfection or cancer upon disease progression and treatment of both HIV and the comorbidities, such as hepatitis B virus (HBV), hepatitis C virus (HCV), tuberculosis (TB), or malaria?
- What are the clinical and public health ramifications of ART in developing countries?
- What types of interventions facilitate the delivery of therapeutic interventions for HIV disease in a resource-poor setting?

**PRECLINICAL
DEVELOPMENT OF
NEW THERAPEUTIC
AGENTS**

PRIORITIES FOR FUTURE RESEARCH:

- **Advance the discovery and validation of new viral and cellular targets.**
- **Develop new therapeutic agents that:**
 - ▶ **target drug-resistant virus;**
 - ▶ **have activity in viral reservoirs and cellular compartments; and**
 - ▶ **have improved pharmacologic and toxicologic properties.**

The NIH sponsors an active and comprehensive drug discovery and development program that permits the design and identification of new, safe, and more effective drugs and drug regimens that target drug-

resistant virus, have activity in viral reservoirs and cellular compartments, and have improved pharmacologic and toxicologic properties. The discovery and validation of new viral and cellular targets is key to the development of next generation and better therapeutic agents and regimens. Collaborations between Government, academia, and industry are essential to ensure continued advances in AIDS drug development research, preclinical development of new agents, and clinical trials. The goal of these programs is to develop therapeutic agents and regimens that slow disease progression, extend life expectancy, and improve the quality of life for HIV-infected individuals in both developed and developing countries.

NIH-sponsored AIDS therapeutics programs provide resources for conducting preclinical testing of potential compounds against HIV infection and its sequelae. Evaluation of the biological properties of these drugs, as well as their pharmacology and toxicology, in model systems permits a better understanding of their potential role in the treatment armamentarium. The importance of these models is further emphasized by the increasing role of drug toxicities and complications in causing significant morbidity and mortality. Additional efforts are essential to accelerate the development and testing of microbicides and of other chemical and physical barriers to halt the sexual transmission of HIV and other sexually transmitted infections (STIs). A separate component of this Plan has been developed for this critical area of NIH-sponsored research. Collaborations between Government-sponsored programs and the pharmaceutical and biotechnology industries are essential in advancing potential microbicial agents through the drug development process.

CLINICAL EVALUATION OF THERAPIES

PRIORITIES FOR FUTURE RESEARCH:

- **Determine optimal therapeutic strategies including when to start (early versus late), change, sequence, or interrupt therapies and evaluate therapeutic drug monitoring strategies.**
- **Identify regimens with improved toxicity, efficacy, pharmacokinetics, activity in viral reservoirs, adherence potential, and reduced cost.**
- **Target affected populations, especially women, injecting drug users (IDUs), children, adolescents, older adults, and across racial/ethnic groups. Conduct studies that permit evaluation of potential differences in response to therapy due to gender and/or racial/ethnic differences.**
- **Enhance capabilities for long-term followup and evaluate the long-term effects of therapy and the implications of these findings on public health.**

- **Conduct studies to evaluate the implications of therapy to prevent HIV transmission on public health.**
- **Identify immunologic correlates of effective viral suppression in the setting of clinical therapeutic intervention trials.**

The widespread use of ART in HIV patient care has resulted in increased life expectancy and improved quality of life for many HIV-infected individuals in the United States and Western Europe since 1996. Sharp declines in AIDS death rates and substantial reductions in the incidence of AIDS-related OIs and some cancers beginning with the use of ART have continued through 2002. Initial sharp declines in new AIDS cases observed in 1996 have leveled off and remained the same since 1999. Unfortunately, a growing proportion of HIV-infected individuals receiving therapy experience treatment failure with ART failing to reduce viral loads. Some patients are unable to comply with complex treatment regimens, experience toxicities and side effects, or cannot afford their high cost. An increase in side effects and complications leading to liver failure, kidney disease, and cardiovascular disease has been observed as HIV-infected individuals continue on drug regimens. One of the highest priorities of NIH-sponsored AIDS research continues to be the clinical evaluation of potential agents and the development of treatment regimens against HIV infection and its associated OIs and malignancies. Clinical research targets the identification of better drugs and treatment regimens to reduce and overcome these limitations, so that HIV-infected individuals can live longer with improved quality of life and delayed disease progression.

The AIDS epidemic in the United States continues to affect diverse communities including women, racial and ethnic minorities, adolescents, substance and alcohol abusers, and older adults. The NIH continues to place a high priority on the recruitment and retention of individuals from these affected populations in clinical trials to the extent that they reflect the ongoing epidemic. Increased enrollment of these communities may permit evaluation of potential differences in response to therapy due to gender and/or racial and ethnic differences.

Clinical trials permit the identification of safe and effective treatment regimens with increased efficacy, decreased toxicity, improved pharmacokinetics, activity in viral reservoirs, and easier adherence. The metabolic and morphologic complications associated with these treatment regimens result in significant morbidity and mortality, thus warranting further investigation. These studies also will help define when to begin, switch, and interrupt drugs within treatment regimens and identify therapies for treatment-experienced individuals who no longer respond to currently available ARVs.

**MOTHER-TO-CHILD
TRANSMISSION**

Clinical findings from NIH-sponsored studies are continuing to provide crucial information leading to better treatment regimens for HIV-infected individuals. The translation of clinical trial results into treatment guidelines and standards of care that can be used by health care providers is critical in bringing results from the “bench to the bedside” and, ultimately, resulting in better care for those affected by HIV disease.

Antiretroviral Interventions for Prevention of Transmission

PRIORITIES FOR FUTURE RESEARCH:

- **Evaluate the effects of short-course ARV prophylaxis regimens, including ART, used for prevention of HIV mother-to-child transmission (MTCT) in domestic and international settings on development of drug resistance and the effects of drug resistance on efficacy of prophylaxis, responses to future ART in women and infants who become infected despite prophylaxis, and develop interventions to prevent development of such resistance in women and infected infants.**
- **Develop safe, effective, feasible, and conveniently administered strategies to interrupt MTCT of HIV with a focus on resource-limited settings and a special emphasis on breastfeeding.**
- **Conduct studies to evaluate and reduce short- and long-term toxicity of ARVs to prevent HIV transmission in women during pregnancy, and in their offspring who were perinatally exposed.**

NIH-sponsored research has identified several effective short-course ARV prophylaxis regimens for use in resource-limited settings that can reduce MTCT by more than 40 percent. Recent studies have shown that resistance can develop rapidly due to a single mutation for two of the drugs used in short-course prophylaxis regimens, lamivudine (3TC) and nevirapine. It is of particular concern that at 6 weeks postpartum, 25 percent of women receiving single-dose intrapartum nevirapine, and 46 percent of infants who become infected, despite single-dose nevirapine prophylaxis, have detectable drug resistance. While this resistance fades from detection by 12 months, it likely remains in the viral reservoir at low levels. Studies need to better define the kinetics of developing drug resistance, as well as evaluate drug resistance in different compartments (e.g., plasma, breast milk, genital fluids). The effects of prior exposure to short-course ARV prophylaxis on subsequent response to ART when required for treatment of HIV-infected women and their infants is not known. This is an important scientific question as ART is implemented in resource-limited settings and non-nucleoside based regimens are often first-line therapy. Additional strategies to prevent the development of drug resistance are needed.

The NIH has placed a priority on the continued development and testing of interventions to halt MTCT of HIV in resource-limited countries, especially transmission occurring through breastfeeding. While there has been success in the United States and many developed nations, MTCT continues to be a significant problem in developing countries and resource-poor settings, particularly settings where breastfeeding is prevalent and replacement feeding is not feasible. A better understanding is needed of the mechanisms, timing, and risk factors for breast milk transmission. Further progress is needed to identify better treatment approaches that can block MTCT, including transmission associated with breastfeeding.

Significant advances have been made in the prevention of MTCT since the success of the Pediatric AIDS Clinical Trials Group (PACTG) protocol 076. Widespread implementation of the PACTG 076 regimen in the United States and Western Europe has resulted in a mother-to-child transmission rate of less than 2 percent for women who are identified antenatally and receive combination ARV prophylaxis, possible elective cesarean delivery, and do not breastfeed. Pregnant HIV-infected women also need ART for their own health. Recent studies have shown higher doses of protease inhibitors may be needed during pregnancy to achieve therapeutic drug levels. It is critical that studies are conducted in resource-rich and resource-limited countries to define the safety and pharmacokinetics of antiviral agents in pregnant and breastfeeding women and neonates; transplacental and breast milk passage of these agents; development of drug resistance; and potential short- and long-term effects of perinatal ARV drug exposure, particularly combination ARV regimens used for treatment of the woman, the infant, and the child.

The development and testing of safe, effective, affordable, and sustainable interventions to inhibit MTCT that can be used in resource-limited settings is a priority. The evidence-based selection of effective regimens remains a challenge in resource-limited settings and in settings where women are diagnosed late in pregnancy or postpartum in developed nations. The widespread use of ARVs in these settings is further complicated by a complex array of challenges including coinfections and endemic diseases, limited availability of health care staff and facilities, and limited capabilities for clinical and laboratory monitoring. Innovative approaches are needed to define and implement effective regimens among such populations.

HORIZONTAL TRANSMISSION

PRIORITIES FOR FUTURE RESEARCH:

- **Evaluate interventions, including ARV and immunotherapeutic, in clinical trials to reduce horizontal transmission during both acute and chronic HIV infection, in domestic and international settings.**
- **Evaluate the risk of resistance on HIV acquisition and transmission during interventional studies designed to reduce horizontal transmission.**
- **Evaluate the public health impact of interventions designed to reduce horizontal transmission.**

It is critical that studies be conducted to evaluate ARV and immunotherapeutic interventions that block horizontal transmission of HIV. An important objective of these interventional studies is to evaluate the risk of resistance on HIV acquisition and transmission. Additional research is needed on the public health impact of interventions to reduce horizontal transmission.

EVALUATION OF COINFECTION

PRIORITIES FOR FUTURE RESEARCH:

- **Evaluate the effects of coinfection, especially with HBV, HCV, TB, or malaria, on the management of HIV. Determine the bidirectional effects of coinfection and treatments on disease progression and drug interactions.**
- **Develop new agents for the treatment of HBV, HCV, TB, and malaria in the setting of HIV infection, with specific attention to pharmacologic drug interactions and nonoverlapping toxicity.**

HCV infection is continuing to spread at an alarming rate in the United States, as well as globally. The continued expansion of the AIDS epidemic in this country into substance abuse and minority communities translates into greater numbers of coinfecting individuals. The NIH continues to place a priority on the development and evaluation of potential therapies for the prevention and treatment of HIV-associated infections and coinfections. A better understanding is needed to determine the bidirectional effects of coinfection and treatments for these coinfections on disease progression and drug interactions. In international settings, hepatitis, TB, and malaria continue to play significant roles as comorbidities of HIV infection. New and better drugs and therapeutic regimens are needed for the treatment of HBV, HCV, TB, and malaria as coinfections of HIV infection, with particular attention to drug-drug interactions and minimizing toxicities.

DEVELOPMENT OF IMMUNE-BASED THERAPEUTICS

PRIORITIES FOR FUTURE RESEARCH:

- **Develop and evaluate therapeutic approaches including vaccines that will improve and sustain immune function or prevent transmission of HIV infection.**
- **Identify and validate immunologic determinants to predict the efficacy of immune-based therapies.**

Recent studies continue to provide crucial insights into the pathogenesis of HIV infection and the role of individual immune factors in containing the infection. While initiation of ART has afforded improvements in restoring immune function and immunologic parameters, further study is needed to determine what therapeutic approaches can improve and sustain immune function. The development of immunologic therapeutic approaches that can prevent transmission of HIV from infected individuals to uninfected individuals is important. Similarly, the identification of immunologic determinants that will predict the efficacy of immune-based therapies is needed.

INTERNATIONAL

PRIORITIES FOR FUTURE RESEARCH:

- **Expand international clinical research programs in countries with limited resources.**
- **Design and conduct clinical studies that are appropriate for diverse international settings.**
- **Design studies to improve and facilitate the delivery of therapeutic and prevention interventions for HIV disease.**
- **Evaluate the clinical and public health impact of ART.**
- **Evaluate the clinical and public health impact of prophylactic and therapeutic interventions for coinfections/OIs, AIDS-related malignancies, and other cancers.**
- **Evaluate prevention strategies in adult and pediatric settings, including those based on microbicides, vaccines, and ARV interventions.**
- **Encourage studies that integrate therapeutic regimens and prevention interventions.**

The NIH has placed a high priority on the conduct of international AIDS research and the development of drug regimens to prevent, treat, and control HIV disease and its coinfections in developed and developing nations. NIH-sponsored studies are conducted in accordance with the highest scientific and bioethical standards. These studies require

the direct involvement of host nation researchers as equal partners in the design, conduct, and analysis of clinical trial protocols. This approach ensures the involvement of the host nation in the conduct of the clinical study, as well as the implementation of therapeutic interventions after the study is completed. Two separate components of this Plan have been developed to address these relevant areas of NIH-sponsored research: Training, Infrastructure, and Capacity Building, and International Research. The increasing urgency of the AIDS pandemic requires that treatment be viewed in the context of other complex and complicating factors: availability of health care resources; trained personnel and infrastructure to provide therapies; coexisting infections; and public health impact. While this represents a significant and daunting challenge, the development of safe, efficacious, sustainable, and affordable treatment regimens must be targeted to all who are affected by HIV disease.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE - A:

Identify and validate viral and cellular functions required for HIV replication that can be targeted for viral inhibition, clearance, and prevention of transmission. Discover and develop novel agents and therapeutic strategies directed against viral and host factors involved in HIV transmission, infection, replication, and persistence.

(The scientific objectives of A and B are of equal weight.)

STRATEGIES:

- Identify, characterize, and validate new and understudied viral and host targets for anti-HIV therapy (e.g., factors involved in viral fusion, entry, integration, transcription, replication, assembly, budding, infectivity, virulence, and pathogenicity). Develop predictive test models, including appropriate lentivirus animal models, to aid in identifying agents and strategies active against these targets.
 - ▶ Develop agents (including natural products) and treatment strategies that target, inhibit, and clear HIV in cellular, anatomical, and organ reservoirs and sanctuaries.
 - ▶ Characterize potential agents, including their preclinical, immunologic, pharmacokinetic, pharmacodynamic, toxicity, and teratogenicity profiles.
 - ▶ Develop new compounds and chemical formulations, including microbicides and other methods, suitable for the genitourinary and gastrointestinal tracts.
 - ▶ Employ whole animal and *ex vivo* organ or tissue models of lentivirus infections to study the biologic and pharmacologic characteristics of therapeutic agents.
- Acquire structural information on HIV and cell constituents involved in HIV infection for the design of potent therapeutic agents with activity against drug-resistant strains. Post lead structures on publicly accessible databases in real time.
 - ▶ Integrate genomics and informatics paradigms, concepts, and methodologies (microchip-based screens and analyzers) into mainstream drug discovery and development of therapeutic entities and strategies.

- ▶ Develop enabling technologies to accelerate and optimize the discovery and development of therapeutic entities and strategies; establish the infrastructure to provide services and reagents needed by the scientific community.
- ▶ Evaluate the intracellular pharmacokinetics and activity of ARV agents in different cell types, different stages of the cell cycle, and in all age groups. Correlate intracellular pharmacokinetic parameters with drug efficacy/toxicity.
- ▶ Develop agents with desirable biopharmaceutical characteristics (e.g., improved bioavailability and tissue penetration to the central nervous system [CNS] and other sanctuaries); develop drug delivery devices or systems that improve the pharmacokinetic profile of therapeutic agents, target specific organs or tissues, reduce toxicities and adverse effects, and result in improved adherence to therapeutic regimens.
- Study the mechanisms and implications of drug resistance and viral fitness; evaluate early markers and genotypic mutations that lead to resistance and cross-resistance.
 - ▶ Advance basic and applied gene-based strategies to treat HIV infection and its complications. Foster new approaches and technologies to optimize gene delivery that results in regulated and persistent gene expression. Optimize *ex vivo* gene delivery and advance new concepts, strategies, and vectors for direct *in vivo* delivery.
 - ▶ Develop mathematical and computer models of HIV infection and therapeutic interventions that stimulate and predict *in vivo* efficacy, toxicity, and other outcomes of drug regimens and clinical trials. Investigate the use of pharmacogenetics in identifying optimum therapies.
 - ▶ Investigate the host cell effects of ARV drugs.

OBJECTIVE - B:

Conduct clinical trials (including the development of new methodologies) in domestic and international settings, especially in resource-developing nations, to: (1) evaluate the short- and long-term safety, efficacy, and effectiveness of therapeutic agents and strategies against HIV infection and transmission; (2) identify optimal and appropriate treatment modalities in treatment-naïve and treatment-experienced HIV-infected individuals; and (3) define, evaluate, and mitigate factors that adversely affect the success of therapeutic strategies against HIV infection. Encourage clinical trial designs that build on epidemiologic studies that advance the understanding of disease pathogenesis and progression. Develop domestic and international partnerships to design and conduct clinical studies where the epidemic is prevalent.

(The scientific objectives of A and B are of equal weight.)

STRATEGIES:

Clinical Trials of Therapeutic Agents

- Conduct clinical trials of potential therapeutic agents and combinations of agents in adults, adolescents, and children to determine pharmacokinetics, tissue bioavailability, antiviral activity, effects on the immune system, safety, and clinical efficacy.
 - ▶ Evaluate optimal combinations of agents selected for antiviral synergy, complementary mechanism of action, minimal toxicity and cross-resistance, simplicity of administration, and tolerability.
 - ▶ Evaluate optimal therapies and strategies for individuals who have acute or recent infection, chronic infection but no prior ART, and those with prior ART including individuals with multiple drug-resistant virus.
 - ▶ Support clinical trials to study:
 - long-term efficacy (including toxicities) of therapeutic strategies;
 - timing, selection, and strategic sequencing of ARV agents to optimize clinical outcome; and
 - effects of structured treatment interruption on virologic, immunologic, and clinical outcome.
 - ▶ Evaluate novel therapeutic modalities (e.g., cell-based, gene-based, and therapeutic vaccine approaches) with state-of-the-art antiretroviral therapies.

- ▶ Evaluate coformulated ARVs.
- ▶ Evaluate the benefits or risks of commonly used complementary agents (herbal, homeopathic, and/or naturopathic) when used concomitantly with ART.

Clinical Trials Enrollment

- Strengthen efforts and implement new approaches to ensure the enrollment and retention of women, adolescents, minorities, IDUs, and older adults in clinical trials to reflect the incidence of the epidemic in these populations.
- Strengthen efforts to evaluate new and existing drug treatment regimens in clinical trials that reflect the demographics of the epidemic, including traditionally underrepresented populations. When appropriate, evaluate potential gender, race, ethnicity, age-specific, and pregnancy-related differences in drug efficacy and safety, including pharmacokinetics, metabolism, tissue absorption, and drug elimination.
 - ▶ Identify and evaluate the viral and host factors, including human genomics, associated with ART failure including malabsorption, drug interactions, drug resistance, drug toxicities, pharmacogenetics, and suboptimal adherence.

Clinical Trial Methodology

- Develop and evaluate standardized virologic, immunologic, and clinical markers to assess drug activity; determine and validate the prognostic value of surrogate markers in response to various therapeutic interventions.
- Design, test, and evaluate methods to improve the retention of individuals in clinical trials.
- Develop, incorporate, and validate appropriate quality-of-life parameters in clinical trials of ARV agents.
- Develop methodology to facilitate cross-protocol analysis and meta-analyses.
- Develop methodology for research on decisionmaking by participants.
- Develop methodology for research on the ethical conduct of clinical trials.

Pharmacology

- Determine the relationship between drug exposure (pharmacokinetics) and outcomes (antiviral effect, immune function, and safety) to facilitate dosing strategies within clinical trials, as well as for individual patient management.
- Investigate drug interactions among commonly used treatments for HIV-related disease and its complications, as well as other substances that may be used by HIV-infected individuals.

Viral Reservoirs

- Evaluate the presence and persistence of HIV in different tissue compartments during ART; investigate the role of anatomic and cellular sanctuaries in the development of HIV drug resistance, transmission, and establishment of long-term reservoirs.
- Evaluate the penetration of ARVs into different tissue compartments (e.g., genital secretions/semen, CNS, breast milk, etc.).

Viral Resistance and Fitness

- Explore the utility of real-time ARV phenotypic and genotypic assays in managing ART across a broad spectrum of individuals.
- Evaluate the impact of transmission of drug-resistant HIV strains on disease progression and therapy.

Adherence

- Support research on the effectiveness of pharmacological approaches, behavioral interventions, and other approaches to facilitate better adherence to ARV regimens.
- Develop better methods to assess adherence to treatment regimens across a variety of affected populations; compare and validate adherence measures in the context of HIV treatment.
- Investigate strategies for managing symptoms that are attributed to therapy, and investigate the relationship between symptom management and improved adherence to ARV regimens.

Coinfection with HBV and/or HCV

- Evaluate the bidirectional effects of coinfection with HBV and/or HCV in HIV-infected individuals. Evaluate the impact of ART on reactivation of hepatitis viruses, treatment of viral hepatitis in coinfecting individuals, transmission of hepatitis viruses, and development of late-stage complications of viral hepatitis.

International

- Enhance the development of international collaborations that will assist in addressing relevant therapeutic research in populations of HIV-infected adults, adolescents, and children.
- Assist developing nations, as appropriate, in technology transfer through training, infrastructure, and capacity building to facilitate the evaluation of ARV agents and other therapies in local settings.
- Assess the barriers to delivery of effective HIV/AIDS health care including treatment and the capability of conducting international therapeutic clinical trials through the establishment or expansion of multidisciplinary clinical centers.
- Develop and evaluate simpler, reliable, user-friendly, and inexpensive assay technologies for monitoring immunologic and virologic status and ARV drug responses that can be used in resource-limited settings.
- Develop standardized clinical indicators to determine when to initiate ART, to monitor response to therapy, and to determine when to change therapy.
- Evaluate other simple and inexpensive surrogate markers of immunologic and virologic responses for use in resource-limited settings.
- Determine acceptable laboratory monitoring for drug toxicity in resource-limited settings.
- Evaluate the efficacy of ART in HIV-infected women following receipt of ARV prophylaxis to prevent MTCT, including the effect of antiretroviral drug resistance mutations that may arise following prophylaxis on the efficacy of subsequent therapy, and develop interventions to reduce the development of such resistance mutations.

- Evaluate the efficacy of ART in infants/children who become infected despite maternal/infant receipt of ARV prophylaxis to prevent MTCT, including the effects of antiretroviral drug resistance mutations that may arise following prophylaxis on the efficacy of subsequent therapy, and develop interventions to reduce the development of such resistance mutations.

OBJECTIVE - C:

Develop strategies to evaluate, prevent, and treat complications and toxicities of antiretroviral treatment in domestic and international settings.

STRATEGIES:

- Evaluate potential delayed or late effects of ART following short-term administration of prophylaxis regimens, as well as during chronic treatment.
- Support research on the pathogenesis and mechanisms of toxicity of drugs used to treat HIV disease.
- Develop and test approaches to prevent or reverse potential metabolic abnormalities (e.g., changes in body composition, development of atherogenicity and endocrine disorders, and changes in bone and muscle structure) based on an understanding of the mechanisms by which ART and/or suppression of HIV replication may affect metabolic processes.
- Integrate metabolic, endocrine, cardiovascular, neurologic, renal, and bone studies into ongoing and planned treatment trials which may provide an opportunity to answer important questions related to potential complications of ART.
- Develop approaches to monitor and evaluate the effects of gender, race, and age on complications of ART.
- Evaluate the impact of nutritional deficits, impaired access to safe drinking water, regionally significant coinfections, and other population- and area-specific factors on complications of ART in developing countries.
- Support research on the interactions of ART on coinfections.
- Evaluate drug interactions with potential clinical significance for HIV-infected individuals, particularly the interactions between ARVs and psychotropic medications; develop strategies to avoid or minimize the clinical impact of these interactions.

OBJECTIVE - D:

Develop and evaluate new agents and strategies for preventing and treating HIV-associated infections and coinfections including diseases unique to or prevalent in domestic and international settings.

STRATEGIES:

Preclinical Discovery and Development

- Identify and validate potential molecular targets for the discovery and development of agents for prevention and treatment of HIV-associated infections. Delineate the structure and function of potential molecular targets of HIV-associated OIs and coinfections.
- Support preclinical drug design and development programs to develop therapies against associated pathogens, especially *Candida*, *Cryptococcus*, *Cryptosporidium*, cytomegalovirus (CMV), HBV, HCV, Kaposi's sarcoma herpesvirus/human herpesvirus (KSHV/HHV-8), human papillomavirus (HPV), JC virus (JCV, the etiologic agent of progressive multifocal leukoencephalopathy [PML]), malaria, *Microsporidia*, *Mycobacterium avium* complex (MAC), *Mycobacterium tuberculosis*, *Pneumocystis*, *Toxoplasma*, and other prominent coinfections, with emphasis on innovative approaches and agents with favorable bioavailability and pharmacokinetics and development of formulations appropriate for use in children.
- Support and encourage mechanism-based screening of novel synthetic compounds and natural products to identify candidate agents for treating OIs and coinfections; provide support for medicinal chemistry, structural databases, resynthesis, and toxicity testing.
- Cooperate with the private sector to increase involvement and investment in anti-OI and anti-coinfection drug discovery and development research, especially in areas where public health needs are substantial; assume full responsibility, when necessary, for the development of potential therapies with high public health relevance and need.

Clinical Trials of Therapeutic Regimens

- Assess the impact of new ARV regimens on the risks for and manifestations of infections associated with HIV/AIDS in adults, adolescents, and children.

- Improve our understanding of the interplay between HIV-associated immune deficiencies and the onset and types of infectious complications.
- Support clinical research in the context of drug abuse treatment to reduce HIV-associated infections among HIV-infected drug users.

Clinical Trial Methodology

- Improve strategies for prevention of multiple infections in the context of ART; determine the optimal timing for initiating/discontinuing prophylaxis for different OIs and coinfections; develop improved strategies to minimize toxicities and the development of drug-resistant microorganisms.
- Develop tools to identify HIV-infected individuals at high risk for development of specific OIs and coinfections, to improve the efficiency of clinical trial design and the risk/benefit ratio of the currently utilized drugs for prophylaxis and for treatment.
- Develop clinically useful assays and methodologies for early and rapid diagnosis of OIs and coinfections, quantitative assessment of microbiological responses, and drug sensitivity testing.

Coinfections

- Study the interaction between HIV infection and infectious complications upon pathogenesis, presentation, and disease outcomes in adults, adolescents, and children.
- Support clinical trials, domestic and international, of adults and children coinfecting with HIV and TB (both active and latent infection). Evaluate safety and efficacy of treatment regimens in coinfecting individuals. Determine optimal length of treatment. Evaluate regimens in the context of degree of immunosuppression (late versus middle versus advanced HIV disease).
- Investigate surrogate markers of TB disease that could distinguish between latent, active, and eradicated infection in coinfecting individuals; determine how each infection influences or alters the other disease in respect to progression and response to therapy.

- Support clinical trials investigating the efficacy and risks of treatment of HCV in individuals who are coinfecting with HIV; determine how each infection influences or alters the other disease in respect to progression and response to therapy.
- Study the interaction of coinfections with HIV transmission (e.g., placental malaria and perinatal infection) and effects on HIV disease progression.

Pharmacology and Toxicology

- Conduct preclinical studies of anti-OI and anti-coinfection drugs (alone or in partnership with industry) to assess their immunologic, pharmacokinetic, pharmacodynamic, toxic, reproductive, and teratogenic effects, as well as transplacental carcinogenicity.
- Support clinical studies to evaluate the safety and pharmacokinetics of existing and experimental agents intended to treat or prevent OIs and coinfections in HIV-infected infants, children, and pregnant women.
- Evaluate drug interactions between anti-TB agents and HIV medications. Support the investigation of new anti-TB agents with fewer side effects, drug interactions, and/or action against multiple drug-resistant TB (MDR-TB).

Adherence

- Support research on the effectiveness of pharmacologic and other approaches in promoting adherence to anti-coinfection regimens.
- Develop formulations, routes of administration, and delivery systems for existing and experimental anti-OI and anti-coinfection drugs appropriate for use in infants, children, and other populations.
- Develop and evaluate interventions to facilitate better adherence to therapies among populations with HIV infection and substance abuse and/or mental illness.
- Investigate strategies for managing symptoms that are attributed to HIV infection, coinfection, and/or therapy, and investigate the relationship between symptom management and improved adherence to ARV regimens.

International

- Conduct clinical trials in adults and children to evaluate agents for the prophylaxis and treatment of HIV-associated OIs and coinfections; target infections shown to cause significant morbidity by epidemiologic studies, and made worse by HIV-induced immunosuppression.
- Develop and evaluate strategies for treatment and prevention of prevalent opportunistic and endemic infections in the context of HIV infection.

OBJECTIVE - E:

Develop, evaluate, and implement strategies for interrupting mother-to-child transmission (MTCT), applicable to resource-limited and -rich countries, with emphasis on strategies to interrupt transmission through breastfeeding, the short- and long-term effects of interventions for interrupting MTCT on the health of women and infants, and development of drug resistance after antiretroviral MTCT prophylaxis and its effect on subsequent antiviral therapy and efficacy in future pregnancies.

(The scientific objectives of E, F, and G are of equal weight.)

STRATEGIES:

Mechanisms of Transmission

- Investigate the mechanisms and timing of MTCT (*in utero*, intrapartum, and postpartum via breast milk) to facilitate and develop targeted drugs/strategies to further decrease MTCT or provide alternatives to currently identified effective strategies.
- Investigate risk factors associated with early and late breast milk HIV transmission (e.g., breast milk viral load, immune factors, mastitis, and exclusive versus mixed breastfeeding).
- Develop reproducible, sensitive, and specific assays to detect and quantitate the amount of cell-free and cell-associated virus in breast milk.

Interventions and Trials to Evaluate Interventions to Reduce Transmission

- Use and/or develop suitable animal models to evaluate novel strategies to prevent transplacental and postpartum breastfeeding transmission of HIV, and to evaluate transplacental passage of ARV agents and their effects on placental function and on fetal development and viability.
- Develop safe and conveniently administered strategies to interrupt MTCT using interventions that are affordable in resource-limited nations, including specific strategies to prevent postnatal transmission of HIV through breast milk by providing prophylaxis to the infant, mother, or both during the lactational period.
- Evaluate the pharmacokinetics of ARV drugs in pregnant women, and the penetration of ARV drugs into breast milk and genital fluids.

- Evaluate strategies for reducing MTCT when maternal antepartum and intrapartum ART is not given or available (e.g., postpartum prophylaxis of the infant only).
- Support international collaborative efforts to conduct clinical trials of interventions to interrupt MTCT.
- Develop and evaluate strategies for reducing the risk of vertical transmission of HIV from pregnant women to their offspring, and evaluate the impact of that intervention on maternal health treatment options; such strategies may include antiviral agents, anti-HIV immunoglobulin, monoclonal antibodies, agents targeted to cellular targets (e.g., blocking cytokine receptors), cell- and gene-based strategies, vitamin supplementation, HIV vaccines, adjuvants, and virucides, alone or in combination.
- Study the effects of ARV regimens used for maternal health indications on the risk of vertical transmission (including postnatal transmission through breast milk).
- Further evaluate the risks and benefits of cesarean delivery for reducing transmission (e.g., evaluate the risk of postpartum morbidity in infected women with elective cesarean delivery and determine whether the additional benefit of cesarean delivery for preventing transmission accrues in women receiving ART).
- Support research and development of new clinical trial designs, statistical methodologies and investigation of biologic markers, surrogates, and/or other outcomes to evaluate the activity, clinical efficacy, or reasons for failure of new agents and approaches in the treatment of HIV-infected pregnant women and their offspring.
- Develop, incorporate, and validate appropriate quality-of-life parameters and methods to measure the relationship between ARV drug adherence and quality-of-life parameters in HIV-infected pregnant women in clinical trials.

Issues Related to Antiretroviral Drug Resistance

- Evaluate the effects of preexisting viral drug resistance in pregnant women on the effectiveness of ARV regimens to prevent MTCT.

- Evaluate the risk for the development of HIV variants with detectable antiretroviral drug resistance in pregnant women who receive different types of ARV prophylactic regimens and the kinetics and durability of such resistance in cell-free and cell-associated virus in plasma, breast milk, and genital secretions.
- Evaluate the risk for development of HIV variants with detectable antiretroviral drug resistance in infants who become infected despite maternal receipt of ARV prophylaxis regimens and the kinetics and durability of such resistance in cell-free and cell-associated virus.
- Evaluate the effects of developing drug resistance following ARV prophylaxis on the health and response to future ART in women and infants who become infected with HIV despite prophylaxis.
- Evaluate the effect of drug resistance developing following ARV prophylaxis in an initial pregnancy on the efficacy of the prophylactic regimen in reducing transmission in subsequent pregnancies.
- Develop and evaluate interventions capable of reducing the risk for developing antiretroviral drug-resistant virus in women receiving ARV prophylactic regimens and in infants who become infected with HIV despite prophylaxis.

Issues Related to Short- and Long-Term Effects of ARV Prophylaxis for Reducing Transmission on Women and Children

- Evaluate the toxicities, pharmacokinetics (including transplacental drug transfer to fetus/infant), and ARV activity of new agents, existing agents, and combinations of agents in pregnant HIV-infected women and their neonates.
- Evaluate the potential mechanism for possible carcinogenic or mutagenic effects of *in utero* ARV exposure.
- Study the effects of ARV regimens used during pregnancy for treatment of maternal HIV disease (as opposed to use only to prevent perinatal transmission) on maternal health and pregnancy outcome.
- Evaluate the short- and long-term clinical, immunologic, and virologic effects of receiving ART during pregnancy for the sole purpose of preventing perinatal transmission in women who choose to discontinue ART after delivery.

- Evaluate the short- and long-term clinical, immunologic, and virologic effects in women receiving ART during lactation, solely to prevent breast milk transmission, but who discontinue treatment following weaning.
- Evaluate the risk of development of laboratory and clinical findings consistent with mitochondrial dysfunction in uninfected HIV-exposed infants with perinatal ARV exposure.
- Support the long-term followup of children exposed to ARVs during pregnancy and/or postpartum to evaluate possible late effects of such exposure.

Implementation Issues

- Develop and evaluate strategies for implementation of effective perinatal transmission prevention interventions in resource-limited and -rich countries, including ways to increase availability and acceptability of prenatal HIV testing and of prophylaxis to prevent MTCT.
- Improve the sensitivity and specificity of diagnostic procedures that are accessible, cost-effective, and have utility in resource-limited and -rich settings to permit the earliest possible determination of HIV infection in infants, and whether ARV and/or immunopreventive therapies affect the timing and sensitivity of these assays for diagnosis.
- Evaluate innovative methods, including rapid HIV antibody testing, to identify HIV infection in pregnant women with unknown HIV serostatus who present in labor and to assess the acceptability of such testing and acceptability and efficacy of ARV prophylaxis to reduce MTCT, when administered to the woman intrapartum and her infant, or to her infant alone.
- Evaluate the public health impact of programs to prevent MTCT.

OBJECTIVE - F:

Evaluate the impact of antiretroviral and immunotherapeutic strategies and their roles in the prevention of horizontal HIV transmission (e.g., sexual, noninjecting drug use, or IDU transmission) in appropriate domestic and international settings.

(The scientific objectives of E, F, and G are of equal weight.)

STRATEGIES:

Mechanisms of Transmission

- Evaluate the influence of drug resistance on the efficacy of ARV regimens to prevent sexual transmission.
- Use and/or develop suitable animal models to evaluate genital and anal passage of ARVs.
- Evaluate the influence of systemic HIV treatment on viral shedding in the genital tract.
- Evaluate the impact of anti-STI treatment on transmission of HIV and HIV shedding in the genital tract.

Interventions to Reduce Transmission

- Support domestic and international collaborative efforts to conduct trials of ARV, immunotherapeutic, and other treatment interventions with an endpoint of horizontal transmission in acute and chronic infection.
- Develop and evaluate strategies for reducing the risk of sexual transmission of HIV without compromising treatment of the HIV-infected individual; such strategies may include antiviral agents, therapeutic vaccines, anti-HIV immunoglobulin, monoclonal antibodies, immunotherapeutic agents, and microbicides, alone or in combination.

Issues Related to ARV Interventions

- Evaluate the risk for developing antiretroviral drug resistance (in cell-free and cell-associated virus, and in sequestered genital or anorectal sites) when using ARVs in interventions to reduce horizontal transmission, including the development of antiretroviral drug resistance in individuals who become HIV-infected while receiving such therapy or in HIV-infected individuals being administered such therapy solely to reduce horizontal transmission.
- Evaluate the public health impact of regimens to reduce horizontal transmission.

OBJECTIVE - G:

Develop and evaluate therapeutic approaches, including therapeutic vaccine candidates, that will restore and sustain a competent immune system in HIV-infected individuals.

(The scientific objectives of E, F, and G are of equal weight.)

STRATEGIES:

- Employ approaches to enhance immune restoration in clinical trials; test specific hypotheses of HIV immunopathogenesis.
- Evaluate the capacity of the immune system to maintain or repair itself after maximal effective viral suppression.
- Evaluate immune-based therapies for the purpose of improving ART-sparing regimens, permitting delay in initiating or reinitiating ART in regimens of analytic treatment interruption (ATI) to identify immune correlates of antiviral control.
- Develop, validate, and standardize new methods for evaluating immune function in clinical trials that enroll adults, adolescents, and children, including assays that may be used in resource-limited settings.
- Accelerate the preclinical and clinical testing of cytokines, modulators of cytokines, and immunoactive agents to prevent further immune deterioration, to reconstitute deficient immune systems, and to enhance the immunogenicity of therapeutic HIV vaccines.
- Develop and evaluate active and passive immunotherapeutic approaches for HIV infection and its sequelae, including the testing of optimum immunogens; determine best patient disease status for response, most effective immunization dose and schedule, and most meaningful readout of clinical impact of the intervention.
- Support research on approaches to facilitate better adherence to immunoactive regimens.
- Evaluate the safety and efficacy of administering cellular immune elements, including use of expanded peripheral blood T cells, bone marrow, cord blood stem cell transplantation, and thymic transplantation.

- Evaluate the immune system after partial restoration by effective ART. Define qualitative and quantitative differences between the restored immune system and the naive immune system to determine if identified deficiencies can be diminished by immunoactive agents including the use of vaccines for specific OIs and coinfections.
- Develop new therapeutic strategies based on gene delivery strategies to protect mature, hematopoietic stem cells, hematopoietic pluripotent cells, and stromal cell elements from destruction by HIV.
- Evaluate the potential to inhibit HIV replication and spread by modifying chemokine receptor expression and/or chemokine levels. Develop agents to block the attachment of HIV to receptors and coreceptors and thus inhibit entry into cells.
- Study the mechanisms of action of immunomodulating agents, and proceed with applied studies and development of the most promising approaches.
- Evaluate immunologic markers that may identify individuals at risk for late complications of therapy.
- Develop standards and definitions to allow better comparisons of late complications across clinical trials.
- Evaluate treatment interruption both to stimulate HIV-specific immune responses and as an analytic readout of treatment effects (ATI).
- Evaluate immune-based therapy as an adjunct to salvage therapy strategies.

OBJECTIVE - H:

Develop strategies for assessing, preventing, and treating HIV nervous system infection and central and peripheral nervous system manifestations of HIV disease.

(The scientific objectives of H, I, and J are of equal weight.)

STRATEGIES:

- Develop and evaluate novel strategies and agents, such as neuroprotective agents, that are active against putative pathways of HIV-induced CNS dysfunction in adults, adolescents, and children.
- Develop and utilize *in vitro* and animal models of CNS lentivirus infections and CNS injury to identify therapeutic agents for the nervous system complications of HIV infection.
- Assess the pathogenic role of viral sequestration in the CNS, including its potential role as a reservoir of viral persistence and as a site of independent selection of antiviral drug-resistant strains and other mutants.
- Design and conduct clinical trials addressing nervous system complications of HIV infection in adults, adolescents, and children.
- Determine the incidence and prevalence of HIV-associated neurologic disease after long-term ART.
- Develop objective quantitative assessments (e.g., surrogate markers in cerebrospinal fluid [CSF] and neuroimaging) of treatment effects.
- Develop therapeutic agents to block HIV entry into the CNS and treat HIV infection in the CNS; evaluate their safety and efficacy in clinical trials.
- Characterize the CNS pharmacokinetics and pharmacodynamics of ARVs; determine the importance of CNS drug penetration, particularly penetration of the blood-brain barrier, in reducing CNS infection in neurologically symptomatic and asymptomatic subjects.
- Develop strategies for manipulating drug transporters at the blood-brain barrier to facilitate entry of ARVs into the CNS compartment.
- Develop better strategies including complementary and alternative medicine therapies to prevent, diagnose, and treat peripheral neuropathies in HIV-infected individuals.

- Conduct studies to determine drug interactions between commonly used treatments for HIV disease and its complications, with treatments for drug abuse and cooccurring mental health disorders.
- Validate and enhance the efficiency of neuropsychological and neurologic tests performed in the context of clinical trials to identify those tests most capable of determining treatment-related changes in different age, racial/ethnic groups, and diverse international settings.
- Determine the prevalence, causes, and pathogenesis of pain in HIV-infected individuals and develop optimal therapies for pain management.
- Monitor CSF for HIV viral load and immune activation markers in individuals enrolled in studies of ART.
- Further elucidate the correlation among CSF HIV viral load, chemokine levels, proinflammatory cytokines, and markers of immune activation with CNS disease in clinical trials.
- Support the research and development of new statistical methodologies, clinical trial designs, and selection and investigation of biologic markers, to evaluate the safety and clinical efficacy of new agents and approaches in the treatment of neurologic complications of HIV disease.
- Support research on the effectiveness of pharmacologic and other approaches to facilitate better adherence to therapeutic regimens in neurologically impaired individuals.
- Evaluate the effectiveness of reducing HIV-associated CNS disease burden by therapeutic agents currently used to treat other neurologic diseases (e.g., Parkinson's and Alzheimer's disease) that may share pathophysiologic features with HIV-associated neurologic disease.
- Develop, incorporate, and validate functional neurologic and quality-of-life scales that are aimed at measuring the impact of nervous system complications of HIV infection in clinical trials.
- Selectively incorporate neurologic and neuropsychological assessments into HIV-related clinical trials.

- Assess the incidence and prevalence of HIV-1 and HIV-2 induced neurological and neurobehavioral complications, and assess the impact of other viral, bacterial, fungal, or parasitic infections on HIV/CNS disease.
- Conduct viral genetic analyses of HIV derived from CNS sources (including studies of the role of HIV-1 non-B subtypes and HIV-2) in causing neurologic and neurobehavioral dysfunction.
- Evaluate host genetic factors that may affect susceptibility to HIV dementia.
- Conduct studies to determine drug interactions between commonly used treatments for HIV disease and its complications, with treatments for drug abuse and cooccurring mental health disorders; develop treatments and regimens that are optimized for HIV-infected individuals with comorbid depression and other psychiatric disorders.

OBJECTIVE - I:

Discover, develop, and evaluate improved strategies for the assessment, treatment, and prevention of cancer-specific manifestations of HIV disease.

(The scientific objectives of H, I, and J are of equal weight.)

STRATEGIES:

Pathogenesis Research and Preclinical Drug Development

- Identify novel mechanisms and targets (e.g., cytokines, angiogenesis factors, viral targets, and hormones) for treatment and prevention of HIV-associated tumors such as Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL), and HPV-mediated lesions and malignancies, including anogenital dysplasias and cancers; develop new therapeutic strategies based on these findings.
- Develop *in vitro* models of KS and assays for angiogenesis inhibitors.
- Promote screening, discovery, and development of novel therapeutic agents with activity against HIV-associated malignancies, including pathogenesis-based strategies, agents with better CNS penetration, and agents with better safety profiles.
- Based upon structural biologic and biochemical information, develop therapeutic agents for the treatment of HIV-associated malignancies.
- Develop preclinical and *in vivo* models (e.g., severe combined immunodeficiency-human [SCID-hu] mice) for the testing of potential therapeutic strategies against HIV-associated malignancies.

Diagnostic Methods

- Improve methods for early diagnosis of malignancies and for early detection of recurrent cancer or secondary malignancies.

Clinical Evaluation of Therapeutic and Prevention Strategies

- Develop therapeutic and prevention strategies for HIV-associated malignancies based on an improved understanding of the role of infectious agents (e.g., KSHV/HHV-8, Epstein-Barr virus [EBV], HPV, and HBV) in their pathogenesis.

- Evaluate novel approaches for the treatment of HIV-associated malignancies through clinical trials, and evaluate the interactions between treatment of malignancies and treatment of the underlying HIV infection.
- Support approaches using gene- and protein-based technologies, such as tissue array and microarray in targeting treatment of HIV-associated malignancies.
- Develop, incorporate, and validate clinical trial methodologies to correlate tumor-specific responses with clinical benefit, including quality-of-life parameters; develop a staging system indicative of prognostic response and survival.
- Identify surrogate endpoints indicative of response to therapy and novel methods for evaluating tumor response including imaging technology.
- Encourage and facilitate collaborative studies within clinical trials networks to develop mechanisms for early identification of individuals at high risk for malignancies. Develop and assess interventional strategies to reduce the risk or prevent the development of malignancies.
- Study the role of immunomodulating agents in the treatment and prevention of AIDS-related tumors.
- Encourage clinical studies of HIV-infected individuals with non-AIDS-defining malignancies. Evaluate the impact of therapy upon virologic, immunologic, tumor parameters, and drug-drug interactions.
- Explore strategies for attenuating or preventing toxicities associated with therapy, and study the effects of such strategies on virologic and immunologic parameters.
- Study the role of *in utero* and long-term exposure to ARVs on the risk of later development of tumors.
- Study populations in resource-limited settings at increased risk of AIDS-related malignancies due to endemic infectious agents (e.g., KSHV/HHV-8) and HPV-associated cervical cancer in women.

OBJECTIVE - J:

Develop and evaluate strategies for the treatment and prevention of serious manifestations of HIV disease including those prevalent in or unique to international settings.

(The scientific objectives of H, I, and J are of equal weight.)

STRATEGIES:

- Develop and evaluate therapeutic strategies for preventing and treating complications of HIV infection, particularly those complications unique to or prevalent in international settings.
- Develop and evaluate conventional and nonconventional chemopreventive approaches, including those containing quantifiable doses of micronutrients (such as vitamins and trace elements) and macronutrients to delay the development of wasting and other complications of HIV disease.
- Evaluate the safety and efficacy of complementary and alternative medicine therapies, including nonpharmacologic interventions such as exercise, nutrition, and sleep cycles, in the management of HIV disease and its complications.

FY 2006 OAR
Therapeutics
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FY 2006 THERAPEUTICS PLANNING GROUP

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